Exhibit C

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Pegaspargase-Induced Pancreatitis

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Background. The purpose of this study is to report the incidence of pancreatitis in patients treated with pegaspargase in our hospital during a 2-year period. *Procedure.* We identified episodes of pancreatitis related to the intramuscular administration of pegaspargase 2,500 IU/m² for the treatment of childhood hematological malignancies during a 2-year period (May 1996–April 1998). Patients were evaluated clinically and by sequential serum amylase and lipase determinations and radiographic examinations. For comparison, episodes of pancreatitis in patients who only received native Escherichia coli L-asparaginase were examined during the same time period. *Results.* Nine children with acute lymphoblastic leukemia (ALL) of 50 (18%) patients who received pegaspargase were diagnosed to have pancreatitis. All had prior therapy with native L-asparaginase. These children developed symptoms consisting of abdominal pain, nausea, vomiting, and decreased appetite within a median of 13 days from the onset of pegaspargase administration. Six patients became symptomatic after their initial dose. Seven patients developed severe or unacceptable toxicity (grades 3 and 4), measured by increased amylase (>2 times normal) and lipase levels or radiographic evidence of pancreatic inflammation or pseudocyst. One patient also developed hyperammonemia and encephalopathy. In contrast, only one out of 52 (1.9%) ALL patients who received native E. coli L-asparaginase during the same time period developed pancreatitis ($P = 0.007$). *Conclusion.* Clinicians should be aware of a possible higher incidence of pancreatitis associated with pegaspargase. Med Pediatr Oncol 34:200–205, 2000. © 2000 Wiley-Liss, Inc.

Key words: pegaspargase - PEG - L-asparaginase; L-asparaginase; pancreatitis; childhood leukemia

INTRODUCTION

L-asparaginase, a well-known and effective chemotherapeutic agent in the management of acute lymphoblastic leukemia (ALL), is an enzyme that hydrolyzes L-asparagine into L-aspartic acid and ammonia, resulting in low plasma and cerebrospinal fluid levels of this amino acid. This depletion results in the inhibition of protein synthesis by malignant cells, such as lymphoblasts, leading eventually to cell death because they are unable to synthesize endogenous L-asparagine [1]. However, normal cells are less affected by the rapid depletion due to their ability to synthesize L-asparagine via induction of the enzyme asparagine synthetase [2]. L-asparaginase (Elspar®, Merck, Sharpe & Dohme, West Point, PA) in combination with vincristine and prednisone induces complete remission in 90 to 95% of children with newly diagnosed ALL [3]. In addition, clinical studies have demonstrated that administering L-asparaginase 9–10 days before methotrexate will potentiate the antitumor activity of methotrexate with lower myelotoxicity [4]. L-asparaginase is also synergistic with high dose cytarabine [5].

The adverse effects of L-asparaginase are related to hypersensitivity reactions and to decreased protein synthesis and include hypoinsulinemia, hypolipoproteinemia, hypoalbuminemia, and deficiencies of coagulation factors and anticoagulants. Organs affected secondary to decreased protein synthesis include the liver, pancreas, and central nervous system [1,6].

Pancreatic dysfunction is a well-recognized toxicity of L-asparaginase causing glucose intolerance in 10% of patients and pancreatitis in 1–16% of patients [2,7–9]. Approximately 2–5% of children experience life-threatening clinical pancreatitis, and 10% will develop transient hyperamylasemia with mild abdominal discomfort, which will resolve in a few days [2].

Polyethylene glycol- L-asparaginase (PEG-Asp) or pegaspargase (Oncaspar®, ENZON, Piscataway, NJ, and Rhone-Poulenc Rorer Pharmaceuticals, Collegeville, PA) is a form of L-asparaginase that has been commercially available since 1994 [10]. Polyethylene glycol (molecular weight 5,000), when conjugated to Escherichia coli L-asparaginase, prevents uptake of the enzyme by the reticuloendothelial system. This in turn decreases the risk of developing antibodies to asparaginase

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and prolongs the circulating half-life of the drug from 1 day to 5–7 days [11,12] with a peak concentration at 72–96 hours after intramuscular (IM) administration using the dose of 2,500 IU/m^2 [13]. Due to the decreased immunogenicity, PEG-Asp can also be substituted for native unmodified L-asparaginase when hypersensitivity has occurred.

Pegaspargase has adverse effects similar to native L-asparaginase, such as hypercoagulability and thrombosis (4%), hyperglycemia requiring insulin therapy (3%), and clinical pancreatitis (1%) (data from ENZON). We report our experience at Loma Linda University Children's Hospital after noticing several cases of pancreatitis among children with acute lymphoblastic leukemia receiving PEG-Asp.

MATERIALS AND METHODS

During the 2-year period from May 1996 to April 1998, the records of all patients who received PEG-Asp were reviewed. PEG-Asp was given IM at the dose of 2,500 IU/m^2.

There were 50 patients (31 males and 19 females) between the ages of 3–15 years; 25 patients had acute lymphoblastic leukemia in first remission, 4 patients had ALL in second remission, 14 had ALL in marrow relapse, 2 had ALL in central nervous system relapse, and 5 had non-Hodgkin's lymphoma in remission. All had prior therapy with native L-asparaginase without development of clinical signs of pancreatitis. One patient was switched to PEG-Asp after developing anaphylaxis to native E. coli L-asparaginase.

All patients were treated according to or entered on Children Cancer Group (CCG) protocols. Seven patients were on CCG 1952 regimen C (augmented Berlin Frankfurt Münster (BFM) with double delayed intensification) for newly diagnosed low risk ALL, 19 on CCG 1961 for high risk ALL, one patient treated according to CCG 1882 for high risk ALL had anaphylaxis to E. coli L-asparaginase, so that he was switched to PEG-Asp; 16 were on CCG 1941 for ALL patients in marrow relapse, two on CCG 1951 for extramedullary relapsed ALL, and five were on CCG 5941 for the treatment of lymphoblastic lymphoma.

Chemotherapeutic agents given concurrently with PEG-Asp or within the preceding 1–2 weeks varied according to the protocol and included during consolidation for newly diagnosed ALL vincristine 1.5 mg/m^2, cyclophosphamide 1,000 mg/m^2, cytarabine 75 mg/m^2, mercaptopurine 60 mg/m^2, and intrathecal methotrexate. During reinduction the relapsed patients received dexamethasone pulses at 20 mg/m^2 orally for 7 days; ifosfamide 1.8 g/m^2, and etoposide 100 mg/m^2 daily for 5 days starting at day 0, methotrexate 1 g/m^2 over 36 hours with folinic acid rescue at day 14; and the combination of methotrexate, cytarabine, and hydrocortisone given intrathecally.

During the same time period, the records of all 52 patients with acute lymphoblastic leukemia who only received native Escherichia coli L-asparaginase were analyzed for episodes of pancreatitis. There were 27 males and 25 females between the ages of 3 months and 18 years. Forty-two patients who were treated according to or entered on CCG 1882, 1901, 1922, 1952 (standard BFM arms), 1953, and 1961 (standard BFM arms) received 15–45 doses of 6,000 IU/m^2 L-asparaginase IM. Ten patients were treated according to or entered on CCG 1882, 1883, 1884, 1901, which included 2–10 doses of 15,000–25,000 IU/m^2.

The diagnosis of pancreatitis was established based on clinical symptoms (steady, epigastric abdominal pain, possibly radiating to the back, that may have been associated with nausea and vomiting) and supported by an increase in serum amylase and lipase levels. The severity of pancreatitis was established according to the CCG criteria based on elevation of serum amylase levels. Normal amylase level was defined as 25–115 U/L. Normal lipase level was 7–45 IU/L. Grade 1 or mild toxicity was defined as < 1.5 times normal ($\times$ N) amylase; grade 2 or moderate, 1.5–2 $\times$ N; grade 3 or severe, 2.1–5 $\times$ N; grade 4 or unacceptable, $> 5 \times$ N. There was no grading for serum lipase elevation. When symptoms started, serum amylase and lipase levels were obtained. If elevated levels were detected, they were followed sequentially until they normalized.

Abdominal ultrasound and computed tomography were obtained in all patients with pancreatitis. Classification of ultrasonographic pancreatic evaluation was as follows: Grade 1 or mild, normal size of pancreas with increased sonolucency; grade 2 or moderate, increased pancreatic size with local increased sonolucency; grade 3 or severe, increased pancreatic size with generalized increased sonolucency; and grade 4 or unacceptable, pseudocyst formation or hemorrhagic pancreatitis.

Incidence of pancreatitis was compared between the two groups using Fisher's exact test. A 95% confidence interval (CI) was calculated for the incidence of pancreatitis.

RESULTS

Pegaspargase-Treated Patients

Nine cases of pancreatitis related to pegaspargase in children with acute lymphoblastic leukemia were documented from the cohort of 50 patients, or 18% (95% CI, 7.5%–28.6%) of the total who received the drug. None of the five children treated with pegaspargase who had diagnosis of non-Hodgkin's lymphoma developed pancreatitis. All cases had previously received at least nine doses of native Escherichia coli L-asparaginase at 6,000 IU/m^2 IM as part of induction without development of

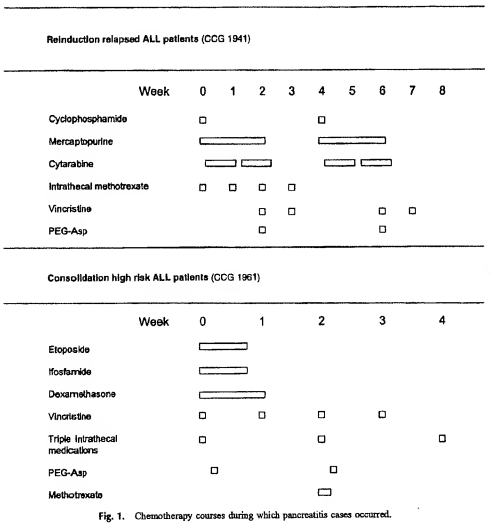

Fig. 1. Chemotherapy courses during which pancreatitis cases occurred.

symptoms related to pancreatitis. Other reasons for pancreatitis such as trauma, infection, biliary duct obstruction, or hypercholesterolemia were not present in these cases.

Concomitant chemotherapy is mentioned in Materials and Methods and shown in Figure 1. Patients 1, 3, 4, 5, 8, and 9 were heavily chemotherapy pretreated since they were in first or second relapse or second remission. In addition, patient number 5 had had bone marrow transplant for marrow relapse 6 months prior, receiving conditioning that included total body irradiation. These six patients received therapy according to CCG 1941. Patients 2, 6, and 7 were relatively less pretreated patients; nonetheless, they were receiving intensive consolidation on study CCG 1961 (augmented BFM with double delayed intensification arm).

Table I summarizes patient data at the onset of symptoms. All patients developed abdominal pain, diffuse or epigastric, and decreased appetite a median of 15 days after PEG-Asp (range 5–44 days). Four patients also developed nausea and vomiting. Six patients (2–6 and 8) had symptoms after the initial PEG-Asp dose.

Table II summarizes the laboratory and radiographic data of these nine children. Seven of them had grade 3–4 toxicities according to amylase elevations. Although there is no grading for lipase elevation, serum lipase levels were consistently higher than the amylase levels. The median lipase level was 10.3 times the normal compared to the median amylase level, which was 2.5 times the normal. Normalization of serum enzyme levels occurred in 6–33 days. The three patients (2, 6, and 7) who had radiographic evidence of pancreatitis had extremely

TABLE I. Clinical Data at Presentation of Pancreatitis

Patient no.	Age/sex	ALL[a] status	Chemotherapy cycle	Number of days between PEG-Asp[b] administration and diagnosis	Signs and symptoms
1	6y/F	Second remission	Intensification	44	Abdominal pain, vomiting, anorexia, diarrhea, lethargy
2	11y/F	First remission	Consolidation	15	Abdominal pain, anorexia, hyperglycemia, DIC[c]
3	14y/M	First relapse	Induction	15	Abdominal pain, nausea, anorexia
4	9y/M	First relapse	Induction	19	Abdominal pain
5	9y/M	Second relapse	Induction	5	Abdominal pain
6	11y/M	First remission	Consolidation	11	Abdominal pain, vomiting, anorexia
7	7y/M	First remission	Consolidation	18	Abdominal pain, anorexia
8	5y/M	First relapse	Induction	5	Abdominal pain
9	16y/M	First relapse	Induction	22	Abdominal pain, vomiting, confusion, seizures, hyperammonemia

[a]Acute lymphoblastic leukemia.
[b]Pegaspargase.
[c]Disseminated intravascular coagulation.

TABLE II. Laboratory Data and Radiographic Findings in Nine Children With Pancreatitis

Patient no.	Highest amylase (U/L)	Grade toxicity	Highest lipase (IU/L)	Number of days till resolution of serum levels	Radiographic imaging of pancreas	Grade toxicity
1	66 (Normal)	0	219 (4.8 × N)	14	Normal	0
2	428 (3.7 × N)	3	1406 (31 × N)	6	Pseudocyst	4
3	300 (2.6 × N)	3	465 (10.3 × N)	17	Normal	0
4	292 (2.5 × N)	3	230 (5.1 × N)	33	Normal	0
5	284 (2.46 × N)	3	253 (5.6 × N)	29	Normal	0
6	254 (2.2 × N)	3	1407 (31 × N)	7	Pancreatic hemorrhage and pseudocyst	4
7	587 (5.1 × N)	4	1764 (39 × N)	17	Increased pancreatic size and edema by CT scan	3
8	212 (1.8 × N)	2	360 (8 × N)	24	Normal	0
9	516 (4.5 × N)	3	499 (11 × N)	14	Normal	0

elevated lipases. These patients (33% of the group having pancreatitis) demonstrated findings in the pancreas by both ultrasound and computed tomography. Two of them had pseudocyst formation persisting for 2 and 9 months.

Further comments on patients 2 and 9. Patient No. 2 was an 11-year-old girl with ALL in first remission who had her highest lipase at 1,406 IU/L and amylase at 428 U/L 15 days after her first pegaspargase administration. She was the only patient with hyperglycemia and one of two patients with radiographic evidence of pseudocyst formation by computed tomography. In addition, she developed disseminated intravascular coagulation (fibrinogen < 50 mg/dl, prolongation of both prothrombin and partial thromboplastin times, fibrin split products of 80–160 ug/ml, and microangiopathic anemia). She required insulin therapy and remained dependent on hyperalimentation for 2 months after the onset of symptoms. She has recovered completely and is still receiving standard maintenance chemotherapy.

Patient No. 9 was a 16-year-old boy with ALL in relapse. He developed pancreatitis after two doses of pegaspargase, along with hyperammonemia (163 umol/L, normal value: 11-45 umol/L), and encephalopathy, consisting of confusion, which progressed to coma. He required intensive care management until his neurologic status improved. He recovered fully within few weeks and eventually received an allogeneic bone marrow transplant.

All patients were managed by discontinuing oral feedings, using nasogastric suction, providing adequate hydration and total parenteral nutrition, and achieving adequate pain control. Patient No. 6 received somatostatin 10 mg/kg subcutaneously every 12 hours in order to decrease pancreatic exocrine production [14] and also required computed tomography-guided external drainage of the pseudocyst due to recurrent bouts of abdominal pain, hyperamylasemia, and enlargement of the pseudocyst. There were no deaths in the group.

Native Asparaginase-Treated Patients

The only patient who developed pancreatitis in the cohort receiving native L-asparaginase was an 18-year

old male with ALL in remission who had received multiple doses of asparaginase at 6,000 IU/m^2 and 7 doses at 25,000 IU/m^2 IM. Other chemotherapeutic agents included daunomycin, thioguanine, cytarabine, and methylprednisolone. He developed abdominal pain 7 days after the last higher asparaginase dose. The highest values of amylase and lipase were 324 U/L (2.8 × N, or grade 4 toxicity) and 782 IU/L, respectively. Increased values persisted for 8 days. His abdominal ultrasound was negative for pancreatic changes. The difference in incidence of pancreatitis between the two groups was statistically significant ($P = 0.007$).

DISCUSSION

Pancreatitis is a well-known complication of Escherichia coli native L-asparaginase [1,6]. Clinical reports vary with the incidence ranging from 1% to 16% [2,7–9]. Several combined studies adding to 1,403 patients revealed 2.5% incidence of clinically apparent pancreatitis [15]. The onset of symptoms may develop during treatment or late being reported to occur up to 16 weeks after native asparaginase administration [9,16]. Clinical symptoms include abdominal pain, nausea, vomiting, and anorexia. Hemorrhagic pancreas and pseudocyst formation can occur. Serum amylase and lipase levels are usually elevated, although in some children they can be normal due to decreased protein synthesis [17]. Reported mortality ranges from 2% to 5% [18].

More recently, PEG L-asparaginase or pegaspargase (Oncaspar®) is being used to treat children with high risk ALL and lymphoblastic lymphoma as part of the initial chemotherapy or when allergic reaction to native asparaginase has occurred. Pharmacological advantages of PEG-Asp over native asparaginase are longer asparagine depletion, less immunogenicity, and less frequent administration [1,13]. This advantage may be clinically beneficial in the treatment of ALL and is presently under investigation.

The incidence of pancreatitis in 18% of the patients who received PEG-Asp is higher than previously reported (0–15%) [2, 19–22] and significantly higher than our own experience with native L-asparaginase (1.9%). Pancreatitis occurred within days and up to 6 weeks after pegaspargase administration (median 15 days). Six episodes presented after the initial dose, resulting in delays in administration of chemotherapy, and significant morbidity including the need for long-term hyperalimentation and recurrent bouts of abdominal pain in three patients, one patient with hyperglycemia requiring insulin, one patient with disseminated intravascular coagulopathy, two patients with pseudocyst, one of whom required percutaneous drainage; and one patient with pancreatitis and encephalopathy. It is unclear whether concomitant administration of other chemotherapeutic agents such as mercaptopurine, vincristine, corticosteroids [9], ifosfamide [23], and cytarabine [24] could potentiate the toxicity from PEG-Asp or be directly related to it. Other commonly used medications that could cause pancreatitis are furosemide, pentamidine, sulfonamides, thiazides, valproic acid, cimetidine, and metronidazole. In extremely rare cases, pancreatitis has been found in patients receiving acetaminophen, cyclosporine, or erythromycin [25,26]. Medications utilized by our patients, prior to the pancreatitis episodes, were trimethoprim/sulfamethoxazole for Pneumocystis carinii prophylaxis, acetaminophen when required for fever, and cimetidine (patient 9).

It is possible that the increased pancreatic toxicity may be due to the longer half-life of PEG-Asp and to prolonged asparagine depletion. Clinical studies with non-hypersensitive patients have shown an 85–100% depletion of serum L-asparagine levels lasting 14 days after intramuscular administration of 2,500 IU/m^2 every other week as part of a multiagent remission induction for ALL [27]. It is also unclear whether a higher incidence of pancreatitis may be related to specific lots of the drug. We had three cases (patients 2, 6, and 7) within a 5-week period; all of them may have received the same lot.

Our results contrast with findings of other reports. Ettinger et al. [19] did not find pancreatic toxicity associated with PEG-Asp. This series of 21 children and young adults with acute lymphoblastic leukemia in relapse received PEG-Asp at a lower dose (2,000 IU/m^2 either IM or intravenously over 2 hours) every 2 weeks during reinduction. Douer et al. [20] reported on the pharmacokinetics of PEG-Asp and clinical response of 14 newly diagnosed adults with ALL after receiving a single intravenous dose of PEG-Asp 2,000 IU/m^2 along with a standard multiagent induction regimen. None of the patients developed pancreatitis, although a high percentage (43%) had transient hyperglycemia [20]. Frankel et al. [21] also reported that only one of 29 adult patients with ALL treated according to Cancer and Leukemia Group B developed pancreatitis after receiving 2–4 doses of PEG-Asp 2,000 IU/m^2.

Of interest, Asselin et al. [22] reported on the relative toxicity between Escherichia coli L-asparaginase 25,000 IU/m^2 IM every week for 30 doses and PEG-Asp 2,500 IU/m^2 IM every 2 weeks for 15 doses in newly diagnosed children with acute lymphoblastic leukemia treated on a multiagent chemotherapy phase III trial. They found seven cases of pancreatitis among 79 patients receiving high dose native asparaginase (8.8%) compared to five cases among 88 receiving PEG-Asp (5.7%). Although there was a higher percentage in the native high dose group, they concluded this was not a statistically significant difference ($P = 0.26$) [22].

Other studies have found a higher rate of pancreatitis. Volkova et al. [23] using PEG-Asp at 2,500 IU/m^2 found

that nine out of 10 children and one out of 15 adults with acute lymphoblastic leukemia developed hypoproteinemia, hepatotoxicity and pancreatitis, with resolution within 10–20 days after discontinuing PEG-Asp [28]. Increased incidence was also found in the Pediatric Oncology Group protocol #9203, which treated patients with acute lymphoblastic leukemia. Using the currently employed dose of PEG-Asp 2,500 IU/m^2 IM, to replace standard dosing of native E. coli L-asparaginase 6,000 IU/m^2 every other day for six doses, the investigators encountered pancreatitis in 15% of their patients. They felt the incidence was high secondary to the combination of PEG-Asp, mercaptopurine, and cytarabine [2].

Clinicians should be aware of a possible higher incidence of pancreatitis associated with pegaspargase. Large prospective multi-institutional clinical studies should provide a definite answer to this observation.

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